

REMARKS

Reconsideration is respectfully requested in view of the foregoing amendments the remarks which follow and the enclosed Rule 132 Declaration.

By this Amendment, claims 25, 34 and 39-44 have been amended. These amendments are fully supported in the as-filed specification.

Claims 24-32 and 34-44 stand rejected under 35 U.S.C. § 102(e) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Valentini et al. U.S. 5,939,323. This rejection is respectfully traversed.

Matrix of hyaluronic acid derivative

Valentini discloses a chemical method encompassing the use of a pore forming agent (NaCl) whereby a hyaluronic acid benzyl ester having a degree of esterification of from 75 to 100% is transformed into a three-dimensional material of interconnected pores which permits cell ingrowth (see column 2, lines 24-60).

According to the definition given in the Wikipedia, see Annex 1 enclosed, “*a porous medium or a porous material is a solid (often called a matrix) permeated by an interconnected network of pores (voids) filled with a fluid (gas or liquid.) Usually both the solid matrix and the pore network (also known as pore space) are assumed to be continuous so as to form two interpenetrating continua such as in a sponge....*”

As reported in Annex 2 from Wikipedia, copy enclosed, “*the porosity of a porous medium.... describes the fraction of void space in the material ... and it is defined by the ratio:*

$$\Phi = V_v / V_T$$

Where V_v is the volume of void space, and V_T is the total or bulk volume of material including both the solid and void component.

This parameter can be also expressed as percentage porosity; the latter parameter is clearly reported by Valentini at column 4, lines 45-47:

“Void volumes for the scaffold can range from 40 to 90%, having pore size ranging from 10 to 100 microns”.

This material therefore does not substantially differ from the spongy material made of the same HYAFF 11 whose SEM photos and properties are reported in Annex 3, copy enclosed. In fact, this material has a porosity overlapping that of Valentini, namely, 80 and 90% and the pore size (10-400 μm) also overlapping the corresponding Valentini range.

The SEM photos contained in Annex 3 clearly disclose the intrinsic and microscopic structure of this spongy and three dimensional material, namely, that the pores **have different sizes** and being interconnected they are **not equally spaced**.

B) In the claimed process, the epithelial cells are grown on a continuous or perforated membrane.

B1) A continuous membrane differs from a three-dimensional material in the following respects:

- it is a bidimensional material and
- it is not porous.

B2) Also, the perforated membrane claimed herein is not anticipated by Valentini in the following respect:

- it is a bidimensional material, whereas Valentini discloses a three-dimensional material.

In addition, in the annexed Declaration it is pointed out that, to one of ordinary skill in the art, the perforation of a material results in a material which is **completely and totally different** from the porous material obtained by Valentini.

In fact, a definition is given in Wikipedia for “perforation”, enclosed herewith as Annex 4.

“Perforation refers to the puncturing of a material with a harder (usually sharp) object to create a hole or aperture. Perforation or microperforation can be created by pins, needles, dies and punch or laser.

In particular, insofar as laser perforation is concerned this web page is linked to the laser manufacturer ORCA, which clearly discloses the results of **a laser perforation, namely, a material provided with holes or apertures wherein said holes or apertures are separated and equally spaced among each other.**

In fact, the perforated membrane of a hyaluronic acid derivative, onto which the intestinal cells are seeded by the process of the claimed invention, also presents almost the same type of apertures or holes as the perforated material with ORCA TECHNIQUE, as it results from a comparison with the photo reported by ORCA and attached to Annex 4 and the SEM photos of the HYAFF 11 perforated membrane LASERSKIN® of enclosed Annex 5.

In view of the foregoing, one of ordinary skill in the art in the field of materials based on hyaluronic acid derivatives, would certainly acknowledge that **no possible overlap exists** between the definition of the porous material of hyaluronic acid ester as given by Valentini and the wording “perforated membrane of a hyaluronic acid derivative” according to the claimed invention, **because of the following substantial differences:**

- a) Valentini discloses a material provided with **interconnected pores**, which are not equally spaced, whereas the perforated membrane used in the process of the invention is a material provided with **holes or apertures separated and equally spaced among each other.**
- b) Valentini discloses a porous material wherein **pores have different dimensions.** By comparison, the **holes or apertures** in the perforated membranes of the instant invention **always have the same size.**

From the above differences still another substantial difference follows directly, namely,

c) the porous material of Valentini is able **to retain** gases, and liquids, while, by contrast, the perforated membrane prepared by the process of the invention, being provided with holes or apertures, are unable to retain liquids, gases or other materials but rather **favors the passage thereof**.

It follows from the above that Applicants completely traverse the Examiner's conclusion that

"perforated membranes read on the porous scaffold of Valentini".

In addition, Applicants respectfully traverse the Examiner's affirmation that the scaffold of Valentini may be a membrane basing her conclusion, in all probability, on the Valentini passage that *"the scaffolds may have any thickness"*.

In fact, according to Valentini it is critical that the scaffold is three-dimensional so that cells grow **inside** the scaffold (see column 2, lines 37-line 59).

The above affirmation by Valentini, therefore, *de facto* excludes the possibility that Valentini encompasses among his various three-dimensional materials membranes since, as is clearly pointed out in the Declaration, cells which are seeded on a perforated membrane or a continuous membrane, such as those of the biological material of the present invention, grow only **on the surface** of the material, therefore, in a **bidimensional manner**. (See difference (d) of the Declaration.)

In addition, Applicants wish to call to the Examiner's attention the following *"distinction"* insofar as the cellular components of Valentini's biological material are concerned.

Intestinal cells

As pointed out in the Declaration, it is known to those of ordinary skill in the art that intestinal epithelial tissue contains at least three types of cells:

(i) enterocytes which are able to form intestinal villi and which are, therefore, responsible for intestinal absorption;

(ii) goblet cells which secrete mucous; and,

(iii) endocrine cells which are part of the glandular structure and are able to secrete various substances such as hormones, etc. (See Annex 6 enclosed, which shows the structure of a villus.)

As can be clearly seen from the results of the example at pages 6 and 7 of the instant specification, the intestinal cells used in the process of the present invention are **enterocytes** cells, since **only** when seeded and grown onto a perforated membrane of a hyaluronic acid derivative do they **show a marked differentiation due to the appearance of numerous microvilli on their surface.**

It follows, therefore, that by the process of the claimed invention and with the biological material thereby obtained it is possible to recover the intestinal epithelial tissue which is **dedicated to the absorption function.**

Valentini only mentions in passing, at column 8, lines 1-8 that among the **several** type of cells which can be seeded with its porous three-dimensional matrix of hyaluronic acid derivative are intestinal cells.

However, the foregoing definition of intestinal cells would not permit one of ordinary skill in the art to distinguish among the specific types of intestinal cells which can be used by Valentini. Moreover, **no specific example** is reported in Valentini which deals with intestinal cells.

As clearly pointed out in the Declaration, the skilled biologist knows very well that enterocytes are **extremely differentiated** epithelial cells and, therefore, they have a completely different function from the other two types of cells, namely, goblet cells and glandular cells.

It follows from the foregoing that the generic wording (*genus*) “intestinal cells” used by Valentini is utterly and completely **unable to anticipate** the specific intestinal cells (*species*) used in the present invention, which results in morphological differentiation as confirmed *by the appearance of numerous microvilli*. (See the example on pages 6 and 7 of the specification.)

Thus, as can be seen by Applicants’ amendments to claims 25 and 39-43, the intestinal cells which are grown are differentiated as confirmed by the presence of the numerous microvilli. **This clearly evidences that the intestinal cells used in the present invention are solely enterocytes.**

Applicants also wish to point out that the generic definition of intestinal cells given by Valentini cannot be said to anticipate the specific type of intestinal cells recited in claim 25, as now amended, since the same Valentini reference, as pointed out by the Examiner, encompasses that cells in general, seeded on its three-dimensional porous matrix, may undergo differentiation. In fact, the passages mentioned in the Valentini specification are only generic statements, and the only example concerning cell differentiation, involves different type of cells, namely, osteoblasts (see column 11, line 30).

For all of the foregoing reasons, Valentini can in **no way** be said to anticipate the claimed invention. Since the claims distinguish over the Valentini disclosure, withdrawal of the rejection is solicited.

Rejection under 35 U.S.C. § 103(a)

Unobviousness over Valentini

Valentini’s teaching, besides not detracting from the novelty of the claimed invention, is quite remote from even suggesting the invention as presently claimed on the following grounds.

As already widely pointed out, according to Valentini it is critical that the matrix be three-dimensional, thus permitting the ingrowth of cells into the scaffold (see column 2, lines 36-58). It follows, therefore, that Valentini teaches the skilled person to seed

cells, which also includes intestinal cells, in a three-dimensional matrix, rather than in a bi-dimensional matrix.

Applicants wish to draw the Examiner's attention to the example at pages 6 and 7 of the instant specification which shows that the intestinal cells (enterocytes), when seeded on a bidimensional matrix as, for example, the perforated membrane of a hyaluronic acid ester, not only grow well but also show a **marked differentiation due to the appearance of numerous microvilli**. By contrast, the cells seeded and grown in a scaffold of a hyaluronic acid ester (HYAFF 11 3D) do **not show any formation of microvilli** and, therefore, do not undergo any differentiation

It follows from the foregoing that a person of ordinary skill in the art from a reading of Valentini **would have been led away** from:

- ❑ even conceiving of the presently claimed invention, which encompasses a process for seeding the intestinal cells, enterocytes, on a continuous or perforated membrane of hyaluronic acid or derivatives thereof, therefore, a **bidimensional matrix**; and
- ❑ even thinking that decidedly better results could be obtained in terms of differentiation of enterocytes by using a bidimensional matrix in place of the three dimensional matrix taught by Valentini.

For the above reasons, Applicants deem that the invention as presently claimed is decidedly unobvious over the misleading teaching of Valentini. Accordingly, since the claimed invention distinguishes over Valentini, withdrawal of the § 103(a) rejection is in order and is respectfully requested.

Unobviousness over Dorigatti in view of Valentini

Dorigatti discloses a composite material formed by the combination of at least two different materials, namely, a three dimensional matrix of non woven tissue associated with a perforated membrane made of a hyaluronic acid ester, wherein **the sole** perforated membrane is directly in contact with the skin (see claim 1, and also page 6, lines 13-19).

The selection of the material recited as the matrix in independent claim 25 employed a Markush expression which clearly **limits the membrane to either a perforated or continuous membrane**. Thus claim 25, as drafted, clearly **excludes** the presence of another or different type of material besides the perforated membrane of hyaluronic acid or a derivative thereof.

In addition, at page 6, lines 15-19 of Dorigatti it only says that *the perforated membrane of hyaluronic acid derivative is compatible with cell growth on its surface*. However, the layer in contact with the skin was **not** previously seeded with any type of cellular components before being applied to the skin, and even beyond that, Dorigatti is unable to even suggest the presently claimed process and the biological materials obtained thereby which contain a specific type of intestinal cells, namely, enterocytes.

Finally, Dorigatti teaches the application of its composite material **without** cellular components and **only** on the skin and not on any other type of epithelial tissue, such as the intestine.

The above deficiencies in Dorigatti's teaching cannot **in any way** be overcome by Valentini.

In fact, although Valentini discloses a biological material which may contain unspecified intestinal cells, as demonstrated previously, he only addresses the use of a three-dimensional matrix of a hyaluronic acid derivative, and does not teach or suggest the use of bidimensional perforated membranes similar to those taught in the composite material of Dorigatti.

It follows from the above that Dorigatti cannot be properly combined with Valentini since no **hint** can be found in Valentini which would motivate the skilled person to choose or select the intestinal cells of the bidimensional matrix such as the perforated membrane portion of Dorigatti's composite material.

In view of the foregoing, besides being untenable for failing to provide any motivation, as mentioned previously, the above prior art combination is also decidedly remote from even suggesting the invention as presently claimed, wherein the **sole**

bidimensional perforated membrane of hyaluronic acid derivative is used for seeding, growing and differentiating specific type of intestinal cells.

For the above reasons, Applicants deem that the present invention distinguishes over the combined teaching of Dorigatti in view of Valentini. Since the rejection under 35 U.S.C. § 103(a) has been overcome, its withdrawal is solicited.

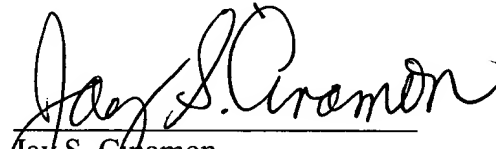
The issuance of a Notice of Allowance is respectfully solicited.

Please charge any fees which may be due and which have not been submitted herewith to our Deposit Account No. 01-0035.

Respectfully submitted,

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